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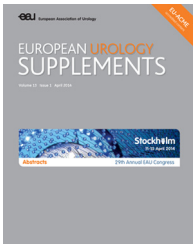

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Genetic Aspects of Congenital Urologic Anomalies

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Abstract

Congenital malformations can be regarded as the result of abnormal foetal development. From a genetic point of view, most congenital malformations are complex genetic disorders. Both genes and environmental factors are important, but their relative impact differs in different malformations as well as individually. Malformations can thus arise through faults in different pathways, resulting in subgroups with different needs for treatment and follow-up.

Most malformations are sporadic and isolated, but if families or relatives are affected, a genetic background is likely. The estimation of the genetic background is based on whether there are affected relatives or families with a Mendelian inheritance, concordance among twins, and association with other malformations or chromosomal aberrations.

In paediatric urology, the genetic influence is especially high in vesicoureteral reflux and hypospadias, with a relative risk of 50 and 20, respectively, among siblings. Genes encoding for these malformations have been identified, especially for hypospadias. Bladder exstrophy is a rare malformation (1:35 000), but the risk for siblings is around 1%, resulting in a comparatively high relative risk. In cryptorchidism, there is an increased incidence among first-degree male relatives. In a small number of cases, there is a monogenetic explanation with mutations in the insulin-like 3 (Leydig cell; *INSL3*) gene and the corresponding receptor. In posterior urethral valves and congenital hydronephrosis, only a few familial cases have been described, indicating a low genetic influence. Improved knowledge of the molecular background of malformations allows for better information and counselling of affected patients and families.

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1. Introduction

When a child is born with a congenital malformation, the parents have four specific questions: Why did this happen to our child? How will it be treated on a short- and long-term basis? What is the short- and long-term prognosis? And finally, can it happen again (ie, will siblings or grandchildren be affected)? Genetic or molecular studies of congenital malformations in children can help answer these questions.

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Table 1 – Signs supporting a genetic background in a malformation

Occurrence of families with Mendelian inheritance of the malformation
Higher relative risk among relatives
Higher concordance among monozygotic twins than among dizygotic twins
Association with chromosomal aberrations
Association with other malformations
Genetic background more common in more severe forms of a malformation

2. The genetic background of congenital malformations

Congenital malformations can be inherited according to the Mendelian laws (ie, autosomal dominant, autosomal recessive, or X-linked recessive, with their respective characteristic inheritance patterns). An example of an autosomal dominant inherited malformation is hand-foot-genital syndrome, which is caused by mutations in the homeobox A13 (*HOXA13*) gene. Congenital adrenal hyperplasia (CAH) is an autosomal recessive inherited disorder in which the 21-hydroxylase deficiency causes virilisation prenatally or later in life. In an X-linked recessive disorder, the males are affected and females are carriers. Because the androgen receptor (*AR*) gene is located on the X chromosome, mutations in the *AR* gene cause undermasculinisation of differing severity in 46,XY individuals, although the mutations are often inherited from a healthy mother.

The vast majority of congenital malformations have a more complex background in that both genetic and environmental factors are involved in the pathogenesis of the malformation (Table 1). For different disorders, the genetic influence can vary along a scale from almost 100% to almost 0% (Fig. 1). A genetic background is suspected, for example, when more than one member of a family is affected. Often there is an association between a more severe form of the malformation and an increased genetic influence. One can estimate the relative impact of the genetic background by comparing the risk for siblings for a certain malformation and the risk for that same malformation in the general population. For hypospadias, for example, the relative risk (RR) for siblings is approximately 30, whereas for type 2 diabetes, it is only approximately 2. Another estimate of the genetic background comes from comparing the concordance rate in mono- and dizygotic twins.

If isolated or recurrent chromosomal aberrations are described in association with a certain disorder, that may indicate certain chromosomal regions with mutations resulting in the disease. Finally, an association with other malformations supports a genetic background or risk factor. Note that a sporadic malformation can be the only symptom of a syndrome with an individually low expressivity, whereas the next sibling can have a more severe phenotype. In the future, with more successful treatment of severe congenital malformations available, the number of inherited malformations is likely to increase.

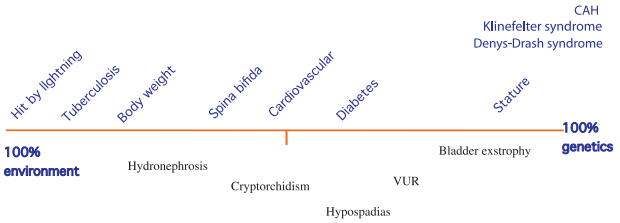

Fig. 1 – Continuum of the influence of genetics versus environment in different disorders and malformations.
CAH = congenital adrenal hyperplasia; VUR = vesicoureteral reflux.

3. Molecular genetic methods

In recent decades, molecular genetic methods have evolved tremendously, and now it is possible to routinely analyse an individual's genes to look for a disease-related mutation. As different methods continue to be used, different molecular mechanisms will be revealed; therefore, sometimes different methods have to be combined to explain a disease mechanism.

The most basic genetic method is karyotyping, used since 1959, and initially used for diagnosing Down syndrome. By karyotyping, chromosome aberrations can be identified with a resolution of approximately 10–15 Mb that may correspond to 50–150 genes. At the beginning of this century, array-based methods were developed to detect submicroscopic chromosomal aberrations, which made it possible to identify smaller chromosomal duplications or deletions, sometimes down to the single-gene level.

Several other methods are used for clinical purposes when there is a specific diagnostic question. DNA sequencing is used in most cases, but other technologies include multiplex ligation-dependent probe amplification, which can identify exon deletions in a gene, or fluorescent in situ hybridisation, when a specific probe for a chromosomal region is used to identify a specific deletion or duplication on one of the chromosomes.

Polymerase chain reaction–based DNA sequencing by the traditional Sanger technique is the dominant method used for clinical purposes when a disease-related gene is known. Massive parallel DNA sequencing (MPS) enables analysing every gene in a patient and has become more accessible mainly for research but also for clinical purposes. Major disadvantages include the demand for bioinformatic support and that all findings still need to be confirmed by ordinary Sanger sequencing. MPS most commonly means sequencing of all exons in the genome, but sequencing of a specific target region or the whole genome also is used.

4. The patient material will determine the study approach

The nature of the malformation determines different situations concerning the patient material, and this will determine which method can be used. If a large family or several rather large families with many affected members are identified, the approach used most in the past was to perform a so-called genetic linkage analysis. By comparing different genetic markers situated on all chromosomes in